Title

Pragmatic randomised controlled trial of periarticular infiltration versus femoral nerve blockade for early pain relief following total knee replacement surgery

Abstract

Aims

To determine the comparative clinical effectiveness of periarticular infiltration versus femoral nerve block for managing early postoperative pain after total knee replacement.

Methods

A pragmatic, single centre, two arm parallel group, participant blinded randomised controlled trial was completed. Patients due for total knee replacement surgery at Hospital [BLINDED] were eligible. Exclusions included contraindications to intervention medications and abnormal lower leg neurology. Participants received either femoral nerve block with 75mg of 0.25% levobupivacaine hydrochloride around the nerve or periarticular knee infiltration with 150mg of 0.25% levobupivacaine hydrochloride, 10mg morphine sulphate, 30mg ketorolac trometamol and 0.25mg of adrenaline all diluted with 0.9% saline to make a volume of 150ml.

Results

264 participants were recruited and data was available on 230 participants (88%) for primary analysis. Intention to treat analysis of the primary outcome for pain (visual analogue scale) on day one prior to physiotherapy was similar between groups; mean difference -0.7, P=0.834 (95% CI -5.9 to 4.5). The periarticular group used less morphine in the first 24 hours compared to the femoral nerve block group (74% 95% CI 55 to 99). The femoral nerve block group reported 39 adverse events (27 serious) in 31 participants and the periarticular group 51 adverse events (38 serious) in 42 participants up to 6 weeks postoperatively. None of the reported adverse events were directly attributed to either of the interventions under investigation.

Conclusion

Periarticular infiltration is a viable and safe alternative to femoral nerve block for early postoperative pain relief following total knee replacement surgery.

Trial registration

The study has been registered with the current controlled trials database under reference number [Blinded].

Introduction

Around 93,000 total knee replacements (TKR) were performed within the National Health Service (NHS) in 2014; a 200% increase since 2004.[1] In the early postoperative phase after TKR surgery, patients can experience substantial pain.[2] Evidence suggests that femoral nerve block, as a single perioperative infiltration of local anaesthetic improves postoperative pain control and reduces the need for systemic analgesics such as opiates.[2] Femoral nerve block is a standard perioperative analgesic regime administered for early relief of pain following surgery.[3] However, femoral nerve block does not provide analgesic effects to the posterior aspect of the knee joint, which is supplied by the sciatic nerve, and so pain relief is often incomplete. Femoral nerve block is also associated with rare but serious complications including damage to the adjacent major blood vessels as well as damage to the nerve itself.[2] In all cases, femoral nerve block temporarily impairs quadriceps muscle function which is important for knee extension, and as a result can lead to falls after surgery.[2,4] Alternative analgesic regimes include an adductor canal block, but this also does not provide analgesic effects to the back of the knee.[5]

A popular alternative approach to femoral nerve block is intraoperative periarticular infiltration of analgesic agents including: local anaesthetics, opiates and non-steroids anti-inflammatory drugs. Periarticular infiltration has the advantage of delivering analgesics directly to the sources of pain, thereby reducing the risk of systemic side effects.[6] Periarticular infiltration can be administered by the operating surgeon without any specialist equipment compared to a femoral nerve block which requires ultrasound or a nerve stimulator or both to be safely administered. In contrast to femoral nerve blockade, periarticular infiltration does not inhibit quadriceps function and can provide analgesia effects to the whole of the knee joint.[2] However, there is limited evidence to support the routine use of periarticular infiltration to control early postoperative pain.[2,7,8]

We report a randomised clinical trial (RCT) comparing periarticular infiltration versus femoral nerve block for patients undergoing TKR surgery to establish the most effective intervention for early (within 24 hours) postoperative pain relief.

Patients and Methods

Study population

This was a single centre, two arm parallel group RCT undertaken at the National Health Service, Hospital [Blinded]. Participants were recruited between December 2013 and October 2015. All patients undergoing an elective primary unilateral TKR were potentially eligible. Our exclusion criteria were:

i. Concomitant medical or psychiatric problems which would prevent completion of treatment or follow-up.
ii. Pre-operative history of neurological abnormality in the ipsilateral leg e.g. history of stoke, neurogenic pain or previous nerve pain.
iii. Specific contraindication to the analgesic agents used.
iv. Participation in a clinical trial of an investigational medicinal product in the last 90 days.
v. Previous entry in the present trial.
vi. Participant unable to adhere to trial procedures.

Randomisation

Participants were allocated to trial treatments through a remote, telephone 1:1 randomisation service using a computer generated randomisation schedule created using randomised blocks and stratified by anaesthetic type (general or spinal). Block sizes were randomly chosen to ensure concealment. Randomisation was undertaken by an independent member of the theatre operating staff on the day of surgery after the participant had received a spinal and sedation or general anaesthetic.

Interventions

All participants were invited to attend the hospitals routine pre-operative TKR education class. Unless contraindicated, participants were given premedication gabapentin. Participants received spinal anaesthetic and sedation or a general anaesthetic. After randomisation participants were allocated to either:

i. Femoral nerve block. The technique involved identification of the femoral nerve below the inguinal ligament using nerve stimulation and/or ultrasound, as per the treating anaesthetist's normal clinical practice and infiltration of 75mg of 0.25% levobupivacaine hydrochloride around the nerve.

Or

ii. Periarticular infiltration The technique involved: 150mg of 0.25% levobupivacaine hydrochloride, 10mg morphine sulphate, 30mg ketorolac trometamol and 0.25mg of adrenaline all diluted with 0.9% saline to make a volume of 150ml. Infiltration of the periarticular mixture was into the skin and soft tissues of the knee by the operating surgeon. The zones of infiltration included: the medial, lateral, suprapatellar and posterior soft tissues structures. Surgeons were advised to infiltrate roughly equal quantities to all four zones.

The fidelity with which both interventions were delivered was reviewed by an independent clinician who observed and audited practice against the intervention protocols described. The results were relayed to those delivering the interventions in order to maintain ongoing protocol compliance.

The remainder of the operation was performed according to the surgeons' routine clinical practice for performing a TKR. All participants followed the same standardised TKR pathway after surgery unless they had specific contraindications; all patients receiving postoperative regular paracetamol, ibuprofen and gabapentin and morphine sulphate sustained release. Oramorph was administered as required and titrated according to participants' pain. Standard hospital prophylaxis for venous thromboembolism (VTE) was administered to all participants unless contraindicated. VTE prophylaxis included: intermittent positive pressure calf compression until mobile and subcutaneous low molecular heparin for 14 days after surgery.

Outcomes

Baseline patient characteristics and preoperative functional status were collected after consent was given. The primary outcome measure was a 100mm visual analogue score (VAS) of pain reported by the patient on the first day after surgery and prior to physiotherapy commencing. The 100mm VAS with 0 being no pain and 100mm being the worst pain is a validated patient reported outcome measure for pain following TKR surgery.[8] The primary end point was chosen after patient feedback indicating that adequate pain relief on the first day after surgery, in preparation for physiotherapy, was of

principal importance to the study population; this is consistent with other smaller RCTs which have also used this time point.[9-11]

Secondary outcome measures were:

i. Pain after physiotherapy on day one postoperatively and pain before and after physiotherapy on day two postoperatively, using the same VAS as the primary outcome

ii. Functional assessment by a physiotherapist using straight leg raise and knee range of movement (ROM) and ability to transfer from bed to chair and time taken to rise from a chair, walk three meters, turn around, walk back to the chair, and sit down (timed up and go)

iii. Total opiate, paracetamol, ibuprofen and gabapentin analgesia used up to 24 and 48 hours after surgery. All opiates were converted to a morphine equivalent dose using a multiplication conversion factor of 0.1 for codeine and tramadol, as outlined in the British National Formulary (BNF).[12]

iv. Oxford Knee Score (OKS) at six weeks after surgery. OKS is a validated self-administered osteoarthritis outcome measure.[13]

v. EuroQol (EQ-5D-5l) at six weeks after surgery. The EQ-5D is a validated measure of health-related quality of life, consisting of a five dimension health status classification system and a separate visual analogue scale.[14,15] The EQ-5D-5L was used and the utility values were calculated using the 3L crosswalk value sets.[16]

vi. Douleur Neuropathic Pain (DN2/Seven Item DN4) Score at six weeks after surgery. DN2 is a tool for assessing neuropathic pain consisting of two questions.[17,18]

vii. Adverse events (AE) up to six weeks after surgery. An AE was defined as any untoward medical occurrence in a participant, which does not necessarily have a causal relationship with the treatment. AEs were further classified into serious adverse events (SAEs) if they fulfilled any of the following criteria: immediately life-threatening, required hospitalisation or prolongation of existing hospitalization, resulted in persistent or significant disability or incapacity, resulted in a congenital abnormality or a birth defect, regarded by the study team as an important medical condition.

Although not reported in this study participants were followed up to 12 months with OKS, EQ-5D-5L, DN2 and AEs.[19] The additional outcome data is being used to help inform the design of a future trial examining chronic pain after TKR surgery.

Blinding

Patients were blind to the intervention to which they were allocated. Allocation concealment was maintained by ensuring randomisation was performed after spinal and sedation or general anaesthetic and then administered within a sterile zone with drapes to physically prevent patients seeing which intervention they received. In addition to ensure postoperative concealment all participants had a standard dressing applied to the area where a femoral nerve block is usually performed. Due to the nature of the study it was not possible to blind the surgeon and anaesthetist delivering the interventions to the treatment options. Outcome data was collected by an independent clinical physiotherapist who was blinded to the treatment allocation.

The trial protocol was prepared in accordance with the Standard Protocol Items: Recommendations for Interventional Trials (SPIRIT) guidelines and published a priori.[19,20]

Statutory research & ethical committee (REC) approval was obtained 23rd September 2013 [Blinded]. The trial was conducted in accordance with the Medicines for Human use (Clinical Trials) Regulations 2004, the International Conference on Harmonisation Good Clinical Practice (ICH GCP) and reported in line with the Consolidated Standards of Reporting Trials (CONSORT) statement.[21]

Patient involvement

Patients were consulted during their routine clinical appointments to determine if the research question was important to them and participants in a successful pilot trial were asked to provide feedback on the trial processes.[20] A small number of pilot trial participants helped to develop the full trial proposal including the choice of primary outcome measure. A patient member was part of the trial steering group and had an active role in overseeing the running of the trial including mechanisms for disseminating the results.

Sample size and analysis plan

The available literature, suggested a between group difference in the VAS of 12 mm (95% CI 9mm-15mm) to be the minimum clinically important difference (MCID).[22] Based upon pilot data, the observed standard deviation for VAS was 30mm.[23] Therefore to test the null hypothesis of equality of the treatment group means, assuming approximate normality for the VAS, 264 patients (132 in each arm) were required for 90% power and 5% significance.

Initial analysis investigated differences in the primary outcome score on an intention to treat basis using an independent samples t-test. The t-test was augmented with a linear regression that adjusted for age, gender and anaesthetic type. Tests were two-sided and considered to provide evidence for a significant difference if p-values were less than 5%. Estimates of treatment effects were presented with 95% confidence intervals. For continuous approximately normally distributed secondary outcome measures (e.g. OKS, EQ-5D), data was analysed in a similar manner to the primary outcome. In hospital medication variables were log transformed prior to testing to better approximate the normal distribution. Count data, such as adverse events, were compared between groups using chi-squared tests.

Some data were not available due to voluntary withdrawal of patients, lack of completion of individual data items or general loss to follow-up. Where possible the reasons for missing data were determined and reported. All analysis presented are based on complete cases.

Analysis was implemented using the software package R.[24]

Results

Participants

From March 2014 to November 2015, 264 patients were recruited, of these 262 were randomised. Two patients were not randomised due to a data entry error. Figure 1 shows the flow of participants from screening, application of eligibility criteria through to final follow up. Baseline characteristics including age, sex, knee function (OKS) and general quality of life (EQ-5D-5L) for both groups of patients was broadly similar, see Table 1.

A total of 59 anaesthetists performed the femoral nerve blocks (median three interventions per anaesthetist, interquartile range one to seven; three operation notes did not list the anaesthetist) and 33 surgeons performed the periarticular infiltrations (median four interventions per surgeon, interquartile range two to 11).

Primary analysis – see* Table *2

On an intention to treat primary analysis the mean treatment difference between groups was not statistically significant; -0.9 (P=0.770, 95% CI -5.3 to 7.2). Using multiple linear regression to adjust for age, gender and anaesthetic type the mean treatment difference between groups was not statistically significant, -0.7 (P=0.834, 95% CI -5.9 to 4.5).

Secondary analysis – see* Table *2 and* Table *3

On day one after physiotherapy mean pain scores increased in both groups, (femoral nerve block group mean=49, periarticular group mean=52, however there was no statistically significant treatment difference between groups; -2.7 (P=0.371, 95% CI -8.6 to 3.2). Mean differences in pain scores on day two both before and after physiotherapy, were also not statistically different between groups, 2.7 (P=0.435, 95% CI -4.2 to 9.7) and 1.8 (P=0.591, 95% CI -4.8 to 8.3) respectively. Figure 2 shows the pain scores on day one and two as box plots.

The proportion of patients able to transfer from bed to chair independently on day one (treatment difference -7.5%; P=0.069, 95% CI -20.7 to 5.7) and the mean time in seconds to get up and go on day two (treatment difference 16.4 seconds; P=0.051, 95% CI -0.1 to 33.0), were both marginally in favour of periarticular infiltration and had borderline statistical significance. The mean knee flexion angle (degrees) at day two was better in the periarticular group, however the difference between treatment arms was small at -5.4 degrees (P=0.005, 95% CI -9.1 to -1.6). Amongst the remaining day one and two functional outcomes there was no significant difference between groups: straight leg raise ability (day one P = 0.192 and day two P=0.219), ability to transfer independently (day one P=0.069 and day two P=0.254) and timed up and go (day one P=0.161 and day two P=0.349).

Analgesic use (total dose in mg) was log-transformed prior to analysis. There was no significant statistical difference up to 24 and 48 hours after surgery in use of paracetamol (P=0.338 and 0.817 respectively), ibuprofen (P=0.285 and 0.309 respectively) or gabapentin (P=0.835 and 0.671 respectively) which were given to all patients as a matter of routine. However, the requirement for morphine which was administered according to participants' pain was less up to 24 hours in those receiving periarticular infiltration (74% of the total dose given to the femoral nerve block group, P=0.042, 95% CI 55 to 99). At 48 hours there was no statistically significant difference in morphine equivalent dose (P=0.203), see Table 3.

At six weeks there was no statistically significant treatment differences in mean EQ-5D (-0.01, P=0.670, 95% CI -0.06 to 0.04), OKS (-0.4, P=0.673, 95% CI -2.4 to 1.5) or DN2 scores (0.4, P=0.118, 95% CI -0.04 to 0.77).

There were two deaths during the trial period. One patient died due to a myocardial infarction, and had been allocated to and received periarticular infiltration, see Table 4. One patient died due to sepsis, and had been allocated to and received a femoral nerve block. There were 51 adverse events (38 serious) amongst 42 participants in the group allocated to periarticular infiltration and 39 (27 serious) amongst 31 participants in those allocated to femoral nerve block, see Table 4. The most frequent adverse events were:

superficial wound infection (15 reports), acute kidney injury (9 reports) and chest infection (8 reports). None of the reported adverse events were directly attributed to either of the interventions under investigation.

Following the primary analysis, we did a post-hoc per protocol analysis for equivalence of outcome. The mean treatment difference was not statistically significant 0.04 (P=0.990, 95%CI -6.2 to 6.3).

Discussion

This trial shows that pain scores the day after TKR surgery are the same between participants who have had a femoral nerve block and those who have had periarticular infiltration. This study was not designed to show equivalence in outcomes, however, the 95% confidence interval limits for the treatment difference, in the per protocol analysis, were only just over half of the pre-specified clinically important difference. We can, therefore be confident that we have excluded a clinically important difference in pain scores on day one between the two interventions.

Although pain scores were similar between groups, the use of morphine pain medication up to 24 hours after surgery was less in those participants allocated to periarticular infiltration. Although morphine is an effective supplementary analgesic for postoperative pain, dose dependent systemic side effects, including nausea, vomiting, respiratory depression, pruritus, reduced gut mobility, and urinary retention mean that lower doses are preferable.[25]

Two other early functional secondary outcomes had borderline significant differences between groups (the ability to transfer independently on day one and knee flexion on day two) and both were in favour of periarticular infiltration. Although caution is needed in interpreting the relevance of the secondary observations these and the primary outcome findings do support the notion that periarticular infiltration is a good alternative to femoral nerve block. Both interventions are designed to provide early analgesic effects and by six weeks we found no evidence of a difference in patient reported outcome measures between the two groups.

None of the reported adverse events were directly attributed to either of the interventions under investigation. Furthermore, the frequency of adverse events was broadly similar in both treatment groups, and were comparable to those reported in the literature, suggesting that periarticular infiltration does not pose any additional risk to patients.[26-28]

Periarticular infiltration has previously been compared to femoral nerve block for early pain relief following TKR surgery in three small RCTs (collectively 181 participants).[9-11] However, meta-analyses (Marques et al 2014 [8], Chan et al 2014 [2] - a Cochrane review – and Albrecht et al 2016[29]) of these RCTs have been unable to draw firm conclusions about the comparative effectiveness of periarticular infiltration versus femoral nerve block largely because of a lack of statistical power and moderate quality (GRADE[30]) evidence. Our results now show that periarticular infiltration offers comparable early pain relief and safety profile. Patients and clinicians should therefore consider other factors including the availability of specialist equipment (e.g. nerve stimulator or ultrasound for administering the femoral

nerve block) and any specific contraindications when making a preference for either intervention.

Strengths and limitations

The main strengths of this trial are patient blinded outcome assessment and its pragmatic design. The trial followed a published protocol and included an intention to treat primary analysis. This means that the findings should be applicable to routine clinical practice.

The main weakness is that the study involved only one centre in the NHS. Although, the trial included many different surgeons and anaesthetists, the study should be replicated in other healthcare settings. The trial has tested only one regime of periarticular infiltration, but others exist including different types of local anaesthetic and dosing. However, the regime we chose and tested was representative of our region and many hospitals throughout the United Kingdom. A data entry error resulted in the final sample for primary analysis being two less than anticipated. However, the evaluated treatment difference of -0.9 is less than the minimum clinically important difference of 1.2, and smaller than the anticipated standard deviation, we are therefore confident that the study is not underpowered and there is no clinical difference between the two treatment arms."

In conclusion there is no clinically meaningful difference in patient perception of pain the day after TKR surgery between those that have a femoral nerve block and those having periarticular infiltration. Periarticular infiltration which can be administered without the need for specialist additional equipment and reduces postoperative morphine requirements should be considered as a viable and safe alternative to femoral nerve block for early pain relief following TKR surgery.

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Competing Interests

All authors have completed the ICMJE uniform disclosure form at www.icmje.org/coi_disclosure.pdf and declare: no support from any organisation for the submitted work; no financial relationships with any organisations that might have an interest in the submitted work in the previous three years; no other relationships or activities that could appear to have influenced the submitted work.

Data sharing

Requests for access to the data will be overseen by the trial steering committee. Reasonable requests will then be given access to a full anonymised dataset.

Transparency statement

The manuscript is an honest, accurate, and transparent account of the study being reported. No important aspects of the study have been omitted; and any discrepancies from the study as planned have been explained.

Tables

Table 1: Baseline characteristics of patients

Patient characteristic	Femoral Nerve Block (n=131)	Periarticular (n=131)
Sex Male, n (%)	51 (38.9)	54 (41.2)
Age, mean (sd)	68.2 (10.0)	68.7 (9.6)
Weight, mean (sd)	82.0 (17.2)	83.2 (17.6)
Smoker Yes, n (%)	13 (10.2)	10 (7.8)
OKS, mean (sd)	23.0 (6.8)	23.5 (7.9)
EQ-5D-5L, mean (sd)	0.5 (0.2)	0.5 (0.2)
Received spinal anaesthetic (remainder received general anaesthetic), n (%)	78 (48)	86 (52)

Table 2: Main outcomes (excluding analgesia use and adverse events)

Outcome		Femoral nerve block	Periarticular	No. of valid responses		P	Treatment difference (95% CI)
				FNB	PI		
Pain score day 1 pre physiotherapy		***44.1 (23.0)***	***43.2 (24.9)***	***113***	***117***	***0.770***	***-0.9 (-5.3 to 7.2)***
Pain score day 1 pre physio; per protocol		43.7 (23.5)	43.7 (24.6)	112	116	0.990	0.04 (-6.2 to 6.3)
Pain score day 1 after physiotherapy		49.0 (22.4)	51.7 (22.0)	108	111	0.371	-2.7 (-8.6 to 3.2)
Pain score day 2 before physiotherapy		40.8 (26.4)	38.1 (24.3)	107	102	0.435	2.7 (-4.2 to 9.7)
Pain score day 2 after physiotherapy		43.3 (24.1)	41.5 (22.6)	100	98	0.591	1.8 (-4.8 to 8.3)
No. able to straight leg raise day 1 (%)		50 (42.4)	61 (51.7)	118	118	0.192	-9.3 (-22.8 to 4.2)
No. able to straight leg raise day 2 (%)		44 (41.1)	53 (50.5)	100	105	0.219	-9.4 (-0.23.7 to 4.9)
Knee ROM day 1 in degrees	Extension angle	-5.4 (7.4)	-3.5 (12.9	118	117	0.174	-1.7 (-4.6 to 0.8)
	Flexion angle	67.4 (18.2)	72.8 (40.9)	118	117	0.197	-5.4 (-13.5 to 2.8)
Knee ROM day 2 in degrees	Extension angle	-4.6 (6.4)	-4.8 (5.6)	111	103	0.848	0.1 (-1.4 to 1.8)
	Flexion angle	73.6 (14.2)	79.0 (13.6)	110	103	0.005*	-5.4 (-9.1 to -1.6)
Ability to transfer day 1	No. independent (%)	44 (36.1)	51 (43.6)	122	117	0.069	-7.5 (-20.7 to 5.7)
	No. assistance of 1 (%)	42 (34.4)	47 (40.2)				-5.8 (-18.8 to 7.3)

	No. assistance of 2 (%) No. unable (%)	15 (12.3) 21 (17.2)	5 (4.3) 14 (12.0)				8.0 (0.3 to 15.7) 5.2 (-4.5 to 15.0)
Ability to transfer day 2	No. independent (%) No. assistance of 1 (%) No. assistance of 2 (%) No. unable (%)	69 (62.7) 30 (27.3) 6 (5.5) 5 (4.5)	76 (72.4) 19 (18.1) 6 (5.7) 4 (3.8)	110	105	0.254†	-9.7 (-23.0 to 3.7) 9.2 (-2.9 to 21.2) -0.2 (-6.7 to 6.1) 1.6 (-5.3 to 6.8)
Timed up and go day 1	Time of those able in seconds	99.3 (51.8)	92.8 (41.8)	61	70	0.436	6.5 (-10.0 to 22.9)
	No. unable (%)	53 (46.5)	40 (36.4)	114	110	0.161	10.1 (-3.6 to 23.9)
Timed up and go day 2	Time of those able in seconds	89.8 (65.8)	73.3 (41.3)	85	90	0.051	16.4 (-0.1 to 33.0)
	No. unable (%)	20 (19.0)	14 (13.3)	105	105	0.349	-13.1 (-5.2 to 16.6)
EQ-5D-5L at 6 weeks		0.8 (0.2)	0.8 (0.2)	122	123	0.670	-0.01 (-0.06 to 0.04)
OKS at 6 weeks		31.0 (7.2)	31.4 (8.2)	120	125	0.673	-0.4 (-2.4 to 1.5)
DNS-2 at 6 weeks		2.0 (1.6)	1.7 (1.4)	102	108	0.118	0.4 (-0.04 to 0.77)

For continuous outcomes, means (standard deviations) are reported and were compared using t-tests. For count outcomes, number (percent of valid) are reported and were compared using $\chi 2$ tests. Analyses are intention to treat unless stated

†to conduct $\chi 2$ test, due to small cell counts "assistance of 2" and "unable" responses have been combined.

* <0.05 therefore reached significance

Table 3: Analgesic use up to 24 and 48 hours (log transformed treatment difference)

Analgesia type and timing		Femoral Nerve Block (n=125)	Periarticular (n=120)	P (transformed t-test)	Treatment difference, % of FNB (95% CI)
Paracetamol in mg, mean (sd)	Up to 24hrs	3524 (689.4)	3533 (620.8)	0.338	82 (50 to 122)
	24 to 48hrs	3720 (929.8)	3791 (818.9)	0.817	94 (55 to 149)
Ibuprofen in mg, mean (sd)	Up to 24hrs	332 (492.7)	265 (436.3)	0.285	67 (30 to 103)
	24 to 48hrs	340.6 (531.8)	301.7 (520.5)	0.309	67 (55 to 103)
Morphine equivalent dose in mg, mean (sd)	Up to 24hrs	62.7 (39.7)	54.8 (39.8)	0.042*	74 (55 to 99)
	24 to 48hrs	40.0 (44.4)	32.5 (28.1)	0.203	82 (55 to 111)
Gabapentin in mg, mean (sd)	Up to 24hrs	492 (354.3)	522 (397.3)	0.835	106 (61 to 182)
	24 to	522.2 (384.7)	580.0 (419.2)	0.671	110 (61 to 201)

	48hrs				

Table 4: Reported adverse events within six weeks of surgery

Adverse event within six weeks	Femoral nerve block	Periarticular	Odds ratio of AE (95% CI)*	P
Death	1	1	1 (0.0 to 79.0)	1
Cement syndrome (perioperative hypotension)	0	1	-	-
Deep wound infection undergoing revision	0	1	-	-
Superficial wound infection	6	9	0.7 (0.2 to 2.1)	0.596
Leaking wound no infection	0	1	-	-
Knee instability undergoing revision	0	1	-	-
Wound haematoma	0	1	-	-
Reduced early ROM (physio only)	1	1	1 (0.0 to 79.0)	1
Reduced early ROM (requiring manipulation)	2	2	1 (0.1 to 14.0)	1
Leg paraesthesia	1	1	1 (0.0 to 79.0)	1
Foot drop	0	1	-	-
Morphine overdose	1	3	0.3 (0.006 to 4.2)	0.622
Acute kidney injury	3	6	0.5 (0.1 to 2.4)	0.500
Chest Infection	6	2	3.1 (0.5 to 31.8)	0.281
Leg swelling (no deep vein thrombosis)	2	2	1 (0.1 to 14.0)	1
Pulmonary embolism	1	0	-	-
Atrial fibrillation	1	0	-	-
Symptomatic anaemia requiring blood transfusion	1	3	0.3 (0.0 to 4.2)	0.622
Bleeding gastric ulcer	1	1	-	-
Vomiting	1	0	-	-
Gastroenteritis	0	1	-	-
Urinary tract infection	1	0	-	-
Urinary retention	1	2	0.5 (0.0 to 9.7)	1
Small bowel obstruction	0	1	-	-
Exacerbation of asthma	1	0	-	-
Leg rash	2	2	1 (0.1 to 14.0)	1
Shingles	1	0	-	-
Leg skin tear	1	0	-	-
Pressure sore	1	0	-	-
Dehydration	1	0	-	-
Admission to manage pain	1	1	1 (0.0 to 79.0)	1
Admission to remove skin clips	0	1	-	-
Admission no cause found	0	1	-	-
General malaise (no cause found)	1	3	0.3 (0.0 to 4.2)	0.622
Back pain	1	0	-	-
Total	**39**	**51**	**0.7 (0.4 to 1.1)**	**0.152**
Classified as SAE	**27**	**38**	**0.6 (0.3 to 1.2)**	**0.152**

* if only one AE then odds ratio not calculated

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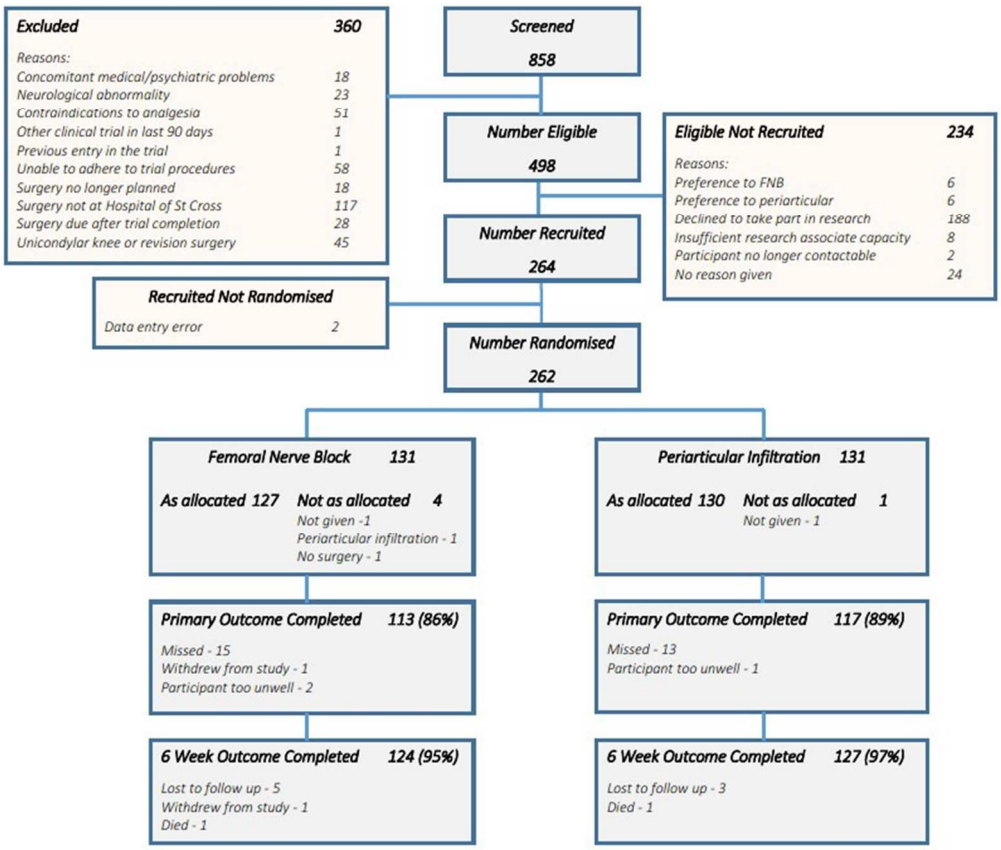

Figure 1: Overall flow of patients within the trial

280x237mm (72 x 72 DPI)

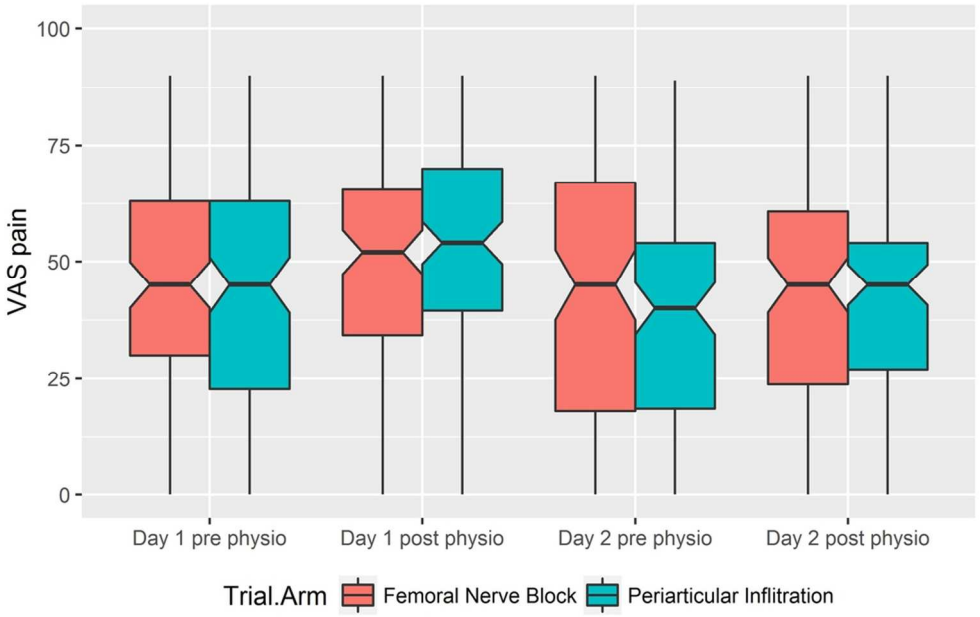

Figure 2: Box plots of pain scores on day 1 and 2

99x66mm (300 x 300 DPI)

CONSORT 2010 checklist of information to include when reporting a randomised trial*

Section/Topic	Item No	Checklist item	Reported on page No
Title and abstract			
	1a	Identification as a randomised trial in the title	1
	1b	Structured summary of trial design, methods, results, and conclusions (for specific guidance see CONSORT for abstracts)	1
Introduction			
Background and objectives	2a	Scientific background and explanation of rationale	2
	2b	Specific objectives or hypotheses	2
Methods			
Trial design	3a	Description of trial design (such as parallel, factorial) including allocation ratio	2
	3b	Important changes to methods after trial commencement (such as eligibility criteria), with reasons	N/A
Participants	4a	Eligibility criteria for participants	2
	4b	Settings and locations where the data were collected	2
Interventions	5	The interventions for each group with sufficient details to allow replication, including how and when they were actually administered	3
Outcomes	6a	Completely defined pre-specified primary and secondary outcome measures, including how and when they were assessed	4
	6b	Any changes to trial outcomes after the trial commenced, with reasons	N/A
Sample size	7a	How sample size was determined	5
	7b	When applicable, explanation of any interim analyses and stopping guidelines	N/A
Randomisation:			
Sequence generation	8a	Method used to generate the random allocation sequence	5
	8b	Type of randomisation; details of any restriction (such as blocking and block size)	2 and 3
Allocation concealment mechanism	9	Mechanism used to implement the random allocation sequence (such as sequentially numbered containers), describing any steps taken to conceal the sequence until interventions were assigned	2 and 3
Implementation	10	Who generated the random allocation sequence, who enrolled participants, and who assigned participants to interventions	2 and 3
Blinding	11a	If done, who was blinded after assignment to interventions (for example, participants, care providers, those	4

		assessing outcomes) and how	
	11b	If relevant, description of the similarity of interventions	N/A
Statistical methods	12a	Statistical methods used to compare groups for primary and secondary outcomes	5
	12b	Methods for additional analyses, such as subgroup analyses and adjusted analyses	5
Results			
Participant flow (a diagram is strongly recommended)	13a	For each group, the numbers of participants who were randomly assigned, received intended treatment, and were analysed for the primary outcome	5 and figure 1
	13b	For each group, losses and exclusions after randomisation, together with reasons	5 and 14 – figure 1
Recruitment	14a	Dates defining the periods of recruitment and follow-up	5
	14b	Why the trial ended or was stopped	5
Baseline data	15	A table showing baseline demographic and clinical characteristics for each group	5 and 8 – table 1
Numbers analysed	16	For each group, number of participants (denominator) included in each analysis and whether the analysis was by original assigned groups	6 and 9 – table 2
Outcomes and estimation	17a	For each primary and secondary outcome, results for each group, and the estimated effect size and its precision (such as 95% confidence interval)	6, 7, 9, 10, 11 – table 2, 3 and 4
	17b	For binary outcomes, presentation of both absolute and relative effect sizes is recommended	6, 7, 9, 10,11 – table 2, 3 and 4
Ancillary analyses	18	Results of any other analyses performed, including subgroup analyses and adjusted analyses, distinguishing pre-specified from exploratory	6, 7
Harms	19	All important harms or unintended effects in each group (for specific guidance see CONSORT for harms)	6, 7, 10 and 11 - table 4
Discussion			
Limitations	20	Trial limitations, addressing sources of potential bias, imprecision, and, if relevant, multiplicity of analyses	7 and 8
Generalisability	21	Generalisability (external validity, applicability) of the trial findings	8
Interpretation	22	Interpretation consistent with results, balancing benefits and harms, and considering other relevant evidence	7 and 8
Other information			
Registration	23	Registration number and name of trial registry	1
Protocol	24	Where the full trial protocol can be accessed, if available	4, 5 and 12

Funding	25	Sources of funding and other support (such as supply of drugs), role of funders	8 - blinded

*We strongly recommend reading this statement in conjunction with the CONSORT 2010 Explanation and Elaboration for important clarifications on all the items. If relevant, we also recommend reading CONSORT extensions for cluster randomised trials, non-inferiority and equivalence trials, non-pharmacological treatments, herbal interventions, and pragmatic trials. Additional extensions are forthcoming: for those and for up to date references relevant to this checklist, see www.consort-statement.org.

The TIDieR (Template for Intervention Description and Replication) Checklist*:

Information to include when describing an intervention and the location of the information

Item number	Item	Where located **	
		Primary paper (page or appendix number)	Other † (details)
	BRIEF NAME		
1.	Provide the name or a phrase that describes the intervention.	1, 2 and 3	
	WHY		
2.	Describe any rationale, theory, or goal of the elements essential to the intervention.	3	
	WHAT		
3.	Materials: Describe any physical or informational materials used in the intervention, including those provided to participants or used in intervention delivery or in training of intervention providers. Provide information on where the materials can be accessed (e.g. online appendix, URL).	N/A	
4.	Procedures: Describe each of the procedures, activities, and/or processes used in the intervention, including any enabling or support activities.	3	
	WHO PROVIDED		
5.	For each category of intervention provider (e.g. psychologist, nursing assistant), describe their expertise, background and any specific training given.	3	
	HOW		
6.	Describe the modes of delivery (e.g. face-to-face or by some other mechanism, such as internet or telephone) of the intervention and whether it was provided individually or in a group.	3	
	WHERE		
7.	Describe the type(s) of location(s) where the intervention occurred, including any necessary infrastructure or relevant features.	3	

	WHEN and HOW MUCH		
8.	Describe the number of times the intervention was delivered and over what period of time including the number of sessions, their schedule, and their duration, intensity or dose.	3	
	TAILORING		
9.	If the intervention was planned to be personalised, titrated or adapted, then describe what, why, when, and how.	N/A	
	MODIFICATIONS		
10.‡	If the intervention was modified during the course of the study, describe the changes (what, why, when, and how).	N/A	
	HOW WELL		
11.	Planned: If intervention adherence or fidelity was assessed, describe how and by whom, and if any strategies were used to maintain or improve fidelity, describe them.	3	
12.‡	Actual: If intervention adherence or fidelity was assessed, describe the extent to which the intervention was delivered as planned.	Figure 1	

** **Authors** - use N/A if an item is not applicable for the intervention being described. **Reviewers** – use '?' if information about the element is not reported/not sufficiently reported.

† If the information is not provided in the primary paper, give details of where this information is available. This may include locations such as a published protocol or other published papers (provide citation details) or a website (provide the URL).

‡ If completing the TIDieR checklist for a protocol, these items are not relevant to the protocol and cannot be described until the study is complete.

* We strongly recommend using this checklist in conjunction with the TIDieR guide (see *BMJ* 2014;348:g1687) which contains an explanation and elaboration for each item.

* The focus of TIDieR is on reporting details of the intervention elements (and where relevant, comparison elements) of a study. Other elements and methodological features of studies are covered by other reporting statements and checklists and have not been duplicated as part of the TIDieR checklist. When a **randomised trial** is being reported, the TIDieR checklist should be used in conjunction with the CONSORT statement (see www.consort-statement.org) as an extension of **Item 5 of the CONSORT 2010 Statement.** When a **clinical trial protocol** is being reported, the TIDieR checklist should be used in conjunction with the SPIRIT statement as an extension of **Item 11 of the SPIRIT 2013 Statement** (see www.spirit-statement.org). For alternate study designs, TIDieR can be used in conjunction with the appropriate checklist for that study design (see www.equator-network.org).

TIDieR checklist